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Epidermal growth factor receptor tyrosine kinase inhibitors as potential cancer chemopreventives

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Abstract

Among the most important targets for chemopreventive intervention and drug development are deregulated signal transduction pathways, and protein tyrosine kinases are key components of these pathways. Loss of tyrosine kinase regulatory mechanisms has been implicated in neoplastic growth; indeed, many oncogenes code for either receptor or cellular tyrosine kinases. Because of its deregulation in many cancers (bladder, breast, cervix, colon, esophagus, head and neck, lung, and prostate), the epidermal growth factor receptor (EGFR) has been selected as a potential target for chemoprevention. Because growth factor networks are redundant, selective inhibition of signaling pathways activated in precancerous and cancerous cells should be possible. Requirements for specific EGFR inhibitors include specificity for EGFR, high potency, activity in intact cells, and activity in vivo. Inhibition of autophosphorylation is preferred, because it should result in total blockade of the signaling pathway. Inhibitors that compete with substrate rather than at the ATP-binding site are also preferable, because they are not as likely to inhibit other ATP-using cellular enzymes. Several classes of specific EGFR inhibitors have been synthesized recently, including structures such as benzylidene malononitriles, dianilinophthalimides, quinazolines, pyrimidines, [(alkylamino)methyl]-acrylophenones, enollactones, dihydroxybenzylaminosalicylates, 2-thioindoles, aminoflavones, and tyrosine analogue-containing peptides. A possible testing strategy for the development of these and other EGFR inhibitors as chemopreventive agents includes the following steps: (a) determine EGFR tyrosine kinase inhibitory activity in vitro; (b) evaluate EGFR specificity and selectivity (relative to other tyrosine kinases and other protein kinases); (c) determine inhibition of EGFR-mediated effects in intact cells; (d) determine inhibition of EGFR-mediated effects in vivo (e.g., in nude mouse tumor xenografts); and (e) determine chemopreventive efficacy in vivo (e.g., in the hamster buccal pouch or mouse or rat bladder). [Journal Article. Review. Review, Academic: 108 Refs; In English; United States]

CAS Registry Numbers: Anticarcinogenic Agents; Transforming Growth Factor alpha; EC 2.7.1.112; Protein-Tyrosine Kinase; EC 2.7.11.-, Receptor, Epidermal Growth Factor

Citation Subset Indicators: Index Medicus

MeSH Terms: Animal; Anticarcinogenic Agents - * pharmacology (PD); Chemoprevention; Human; Neoplasms - etiology (ET), metabolism (ME), * prevention & control (PC); Protein-Tyrosine Kinase - * antagonists & inhibitors (AI); Receptor, Epidermal Growth Factor - drug effects (DE), * physiology (PH); Signal Transduction - * drug effects (DE); Transforming Growth Factor alpha - physiology (PH)

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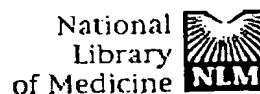
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1: J Pathol. 1992 Jan;166(1):7-12.

Related Articles, Links

The epidermal growth factor receptor in human pancreatic cancer.

Lemoine NR, Hughes CM, Barton CM, Poulson R, Jeffery RE, Kloppel G, Hall PA, Gullick WJ,

Molecular Pathology Laboratory, Hammersmith Hospital, London, U.K.

The epidermal growth factor receptor (EGFR) and its ligands are thought to be important in the control of proliferation of many epithelial systems, including the exocrine pancreas. Abnormalities in expression of two of the known ligands of the EGFR, transforming growth factor alpha and epidermal growth factor, occur frequently in ductal adenocarcinoma of the human pancreas. We have examined an archival series of cases of pancreatic pathology for expression of the EGFR using the anti-EGFR antiserum 12E and found that there is almost ubiquitous overexpression of EGFR in pancreatic cancer and in chronic pancreatitis. Southern blot analysis showed no evidence of amplification or rearrangement of the EGFR gene. We conclude that an autocrine loop involving the EGFR system may be involved in the genesis of both neoplasia and reactive hyperplasia of pancreatic ductal epithelium.

MeSH Terms:

- Adenocarcinoma/chemistry*
- Chronic Disease
- Human
- Neoplasm Proteins/analysis*
- Pancreas/chemistry
- Pancreatic Neoplasms/chemistry*
- Pancreatitis/metabolism
- Receptor, Epidermal Growth Factor/analysis*
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Substances:

- Neoplasm Proteins
- Receptor, Epidermal Growth Factor

PMID: 1538276 [PubMed - indexed for MEDLINE]

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Vascular endothelial growth factor, a multifunctional polypeptide

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Abstract

Angiogenesis, the sprouting of new blood vessels from pre-existing vessels, is a complex, multicellular phenomenon involving capillary endothelial cell (EC) proliferation, migration, and tissue infiltration. The elucidation of the biochemical and molecular factors which control angiogenesis is fundamental to our understanding of normal blood vessel development, as well as of the pathogenesis of abnormal blood vessel formation. Angiogenesis is associated with numerous physiological processes, including embryogenesis, wound healing, organ regeneration, and the female reproductive cycle. However, abnormal angiogenesis also plays a major role in the pathogenesis of tumor growth, rheumatoid arthritis, atherosclerosis and various retinopathies. The cellular and molecular mechanisms underlying both physiological and pathophysiological angiogenesis are only now beginning to be understood. Vascular endothelial growth factor was initially discovered as an unidentified tumor-derived factor which increased microvascular permeability (vascular permeability factor, VPF). Subsequently, it was determined that the protein exhibited mitogenic effects on endothelial cells, but not other cell types. Multiple receptor subtypes have been described which may in part explain the multiplicity of biological actions that have been ascribed to VEGF/ VPF in the literature. In this overview, we briefly summarize what is currently known about VEGF and VEGF receptor biology, as well as VEGF receptor signal transduction mechanisms in endothelial cells. [Journal Article, Review, Review, Tutorial; 111 Refs; In English; Puerto Rico]

CAS Registry Numbers: Angiogenesis Factor; Receptors, Growth Factor

Citation Subset Indicators: Index Medicus

MeSH Terms: Amino Acid Sequence; Angiogenesis Factor - chemistry (CH), * physiology (PH); Endothelium, Vascular - drug effects (DE); Exons - genetics (GE); Female; Gene Expression Regulation - genetics (GE); Human; Male; Molecular Sequence Data; Molecular Weight; Receptors, Growth Factor -

chemistry (CH), physiology (PH); Signal Transduction

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